UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/772,103	01/26/2001	Beatriz M. Carreno	GNN-009CP	7957

7590 01/28/2004

Finnegan Henderson Farabow Garrett & Dunner LLP
1300 I Street N W
Washington, DC 20005-3315

EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 01/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/772,103	CARRENO	
	Examin r	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cov r sh t with th correspond nc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-11 and 13-24* is/are pending in the application.

4a) Of the above claim(s) *16-23* is/are withdrawn from consideration.

5)☒ Claim(s) *14 and 15* is/are allowed.

6)☒ Claim(s) *2-11, 13, 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's submission filed on 10/29/03 has been entered.

Claims 1 and 12 has been canceled.
Claim 24 has been added.

Claims 2-11 and 13-24 are pending.

Claims 2-11, 13-15 and 24 are under consideration in the instant application.

Claims 16-23 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction requirement in Paper No. 11.

2. This Office Action will be in response to applicant's arguments, filed 10/29/03.
The rejections of record can be found in the previous Office Actions.
It is noted that New Grounds of Rejection are set forth herein.

3. The disclosure stands objected to because of the following informalities: "Blanks" are present in the specification on pages 4, 5 and 28 for ATCC and hybridoma designations of the CTLA4 antibodies.

Applicant's previous request to hold correction in abeyance until such time as the ATCC designations can be provided has been acknowledged.

Appropriate correction is required but held in abeyance.

Note that the non-elected claim 20 similarly recites blanks in designating hybridomas.

4. Applicant's cancellation of claim 1 has obviated the previous objection to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

5. A) Applicant's cancellation of claim 1 has obviated the previous rejection of claim 1 under 35 U.S.C. 112, second paragraph, with respect to the recitation of "costimulatory receptor".

B) Applicant's previous amendment of claim 7 has obviated the previous rejection of claim 7 under 35 U.S.C. 112, second paragraph Claim 7 with respect to the recitation of "compared to an antibody without the substitution of amino acid 83".

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 7 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The following *written description* rejection is set forth herein. *This is a New Matter rejection for the following reasons*:

Applicant's arguments, filed 10/29/03, have been fully considered but are not found convincing essentially for the reasons of record.

Applicant argues in conjunction with certain legal decisions that the specification as filed provides sufficient written description for the claimed invention, including the disclosure of representative antibody species to support the claimed genus of anti-CTLA-4 antibodies.

Again applicant's asserts that no New Matter has been added and points to the specification at page 78, line 19 to page 79 at line 13, page 5 at lines 22-25 and to Figure 2B for support for the newly added limitation "results in reduced binding of the antibody by at least about 80% compared to an antibody without the substitution of amino acid 83".

As noted previously and herein, this limitation has been interpreted to compare antibody binding to CTLA4 with and CTLA4 without the position 83 substitution. However, the specification still does not appear to provide an adequate written description of the instant limitation.

Again, applicant points out that Figure 2B shows ELISA results indicating that binding of antibody 26 to the E46 CTLA4 mutant (which using the numbering set forth in SEQ ID NO:2 corresponds to a substitution in amino acid 83) is reduced by about 80% compared to binding of antibody 26 to wildtype CTLA4.

The Examiner acknowledges that data in Figure 2. However, the data are for a single species of antibody, antibody 26. Instant claim 7 is drawn to a genus of antibodies having the same binding properties as a single species of CTLA4 antibody. While the disclosure sets forth the genus of antibodies to CTLA4 and provides one species with the instantly recited properties; the examiner was unable to identify adequate written support in the specification for the now claimed subgenus of CTLA4 antibodies.

Although the specification provides for certain anti-CTLA-4 antibody epitopic specificities, there is insufficient written description to support the genus of "antibody-toxic moiety conjugates of claim 2, wherein the substitution of amino acid 83 in the amino acid sequence of human CTLA4 shown in SEQ ID NO:2 results in reduced binding of the antibody by at least about 80% compared to a human CTLA4 without the substitution of amino acid 83". The instant claim recites characteristics or properties (e.g. "results in reduced binding of the antibody by at least about 80% compared to a human CTLA4 without the substitution of amino acid 83) that are attributed to a particular anti-CTLA-4 antibody.

Further, it is unclear where the written support "at least about 80%" is provided by the specification as filed.

Disclosure of a genus and species of subgenus within that genus is not sufficient description of subgenus to satisfy description requirement of 35 U.S.C. 112, unless there are specific facts which lead to determination that subgenus is implicitly described. Ex parte Westphal, 26 USPQ2d (BPAI 1993). In re Smith 173 USPQ 679 (CCPA 1972).

The instant claims now appear to recite limitations which were not clearly disclosed in the specification and claims as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the present claims, which did not appear in the specification or original claims, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the New Matter in the response to this Office Action.
Alternatively, applicant is invited to clearly point out the written support for the instant limitations.

8. Applicant's cancellation of claim 1 has obviated the previous rejections under 35 U.S.C. 112, first paragraph, written description and scope of enablement.

Claim Rejections – 35 U.S.C. §§ 102 and 103

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:
A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Applicant's cancellation of claim 1 has obviated the previous rejection under 35 U.S.C. 102(b) as being anticipated by Godfrey et al. (U.S. Pat. No. 5,821,332).

12. Claims 2-7, 10-13 and 24 are rejected under 35 U.S.C. 102(e) as being anticipated by Korman et al. (US 2002/0086014 A1) (see entire document).

Korman et al. teach anti-CTLA-4 antibodies, including monoclonal and humanized antibodies, including conjugating therapeutic moieties, including chemotherapeutics and toxins to said antibodies (e.g. abrin, ricin, pseudomonas exotoxin and diphtheria toxin' see page 16 and paragraph 0172 and pages 18-19, paragraphs 0194-0195) (see entire document, including Detailed Description of the Invention). In addition, Korman et al. teach anti-CTLA-4 antibodies that block or antagonize signals transduced by human CTLA-4, including interactions between CTLA-4 and B7 (e.g., see paragraph 0102 on page 8). Given such inhibitory properties of anti-CTLA-4 antibodies, the claimed specificity and functional properties recited in claims 5-7 are inherent properties of the prior art inhibitory anti-CTLA-4 antibodies.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced anti-CTLA-4 antibody conjugates.

13. Claims 2, 10, 11, 13 and 24 are rejected under 35 U.S.C. 102(e) as being anticipated by Lowman et al. (U.S. Patent No. 5,994,511) (see entire document).

Lowman et al. teach antibodies against a variety of antigens, including CTLA-4 (see column 29, paragraph 1), including monoclonal and humanized antibodies (see columns 31-57) as well as Immunoconjugates (e.g., diphtheria A chain, ricin, abrin, see column 43) (see entire document, including Detailed Description of the Invention).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced anti-CTLA-4 antibody conjugates.

14. Claims 2-11, 13 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Korman et al. (US 2002/0086014 A1) AND/OR Lowman et al. (U.S. Patent No. 5,994,511) and further in view of Hamann et al. (U.S. Pat. No. 5,773,001, of record).

Korman et al. teach anti-CTLA-4 antibodies, including monoclonal and humanized antibodies, including conjugating therapeutic moieties, including chemotherapeutics and toxins to said antibodies (e.g. abrin, ricin, pseudomonas exotoxin and diphtheria toxin' see pages 18-19, paragraphs 0194-0195) (see entire document, including Detailed Description of the Invention). In addition, Korman et al. teach anti-CTLA-4 antibodies that block or antagonize signals transduced by human CTLA-4, including interactions between CTLA-4 and B7 (e.g., see paragraph 0102 on page 8

Lowman et al. teach antibodies against a variety of antigens, including CTLA-4 (see column 29, paragraph 1), including monoclonal and humanized antibodies (see columns 31-57) as well as Immunoconjugates (e.g., diphtheria A chain, ricin, abrin, see column 43) (see entire document, including Detailed Description of the Invention).

Lowman et al. differs from the claimed invention by not disclosing human CTLA-4 and the known interactions of CTLA-4 with B7

As noted herein, Korman et al. teach human CTLA-4 as a target of anti-CTLA-4 antibodies as well as the inhibitory anti-CTLA-4 antibodies that antagonize CTLA-4:B7 interactions. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the teachings of Korman et al. to that of Lowman et al. to generate anti-CTLA-4 antibodies that bind human CTLA-4 as well as to generate antagonistic anti-CTLA-4 antibodies. Given such inhibitory properties of anti-CTLA-4 antibodies, the claimed specificity and functional properties recited in claims 5-7 are intrinsic properties of the prior art inhibitory anti-CTLA-4 antibodies.

Both Korman et al. and Lowman et al. differ from the claimed invention by not disclosing the known carbohydrate toxic moiety calicheamicin.

Hamann et al. teach that calicheamicin is a potent toxin that can be conjugated to antibodies, including humanized antibodies, and used to eliminate cells expressing the antigen recognized by the antibody of the conjugate (see entire document, especially "Background of the Invention" at columns 6-20).

One of ordinary skill in the art at the time the invention was made would have been motivated to select from the various known toxic moieties, including carbohydrates such as calicheamicin, bacterial products such as ricin A chain and saporin and chemotherapeutics in combining anti-CTLA-4 antibodies and toxic moieties to target CTLA-4-expressing cells and interactions in various modalities to treat human diseases (e.g. see Methods and Uses of the Invention on pages 22-26 of Korman et al.). From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. Claims 2-11, 13 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Godfrey et al. (U.S. Pat. No. 5,821,332, of record) and Kuchroo et al. (U.S. Pat. No. 6,207,156, of record) , and further in view of Hamann et al. (U.S. Pat. No. 5,773,001, of record) for the reasons of record.

Applicant's arguments, filed 10/2403, have been fully considered but have not been found convincing. Applicant argues that there no reasonable expectation of success nor motivation in combining the cited references.

Applicant's arguments and the examiner's rebuttal are essentially the same of record.

Applicant argues that the teachings of Hamann et al. do not compensate for the deficiencies of Godfrey et al. and Kuchroo et al.

Applicant argues that there is not motivation to combine the teachings of Godfrey et al. with that of Kuchroo et al. because Godfrey et al. teach antibody-toxin conjugates for the purpose of eliminating cells and suppressing an undesired immune response, while Kuchroo et al. teach that anti-CTLA4 antibodies are useful as immune response enhancers.

The claims are drawn to an antibody-toxic moiety conjugate comprising a humanized monoclonal antibody that specifically recognizes human CTLA4, including wherein the antibody blocks binding of CTLA4 to CD80 or CD86.

As previously noted, Godfrey et al. teach the human polypeptide ACT-4 and that this receptor is expressed only on the surface of activated CD4 T cells, its expression being absent on resting T cells as well as on other cell types in physiological conditions (see entire document, but especially columns 9-10 and in particular column 10 at lines 11-17).

Godfrey et al. also teach antibodies to the human ACT-4 protein, including monoclonal antibodies and humanized monoclonal antibodies (see especially columns 14-18).

Godfrey et al. teach that the anti-ACT-4 antibodies can be conjugated to a toxic moiety for use as an immunotoxin (see especially the bridging paragraph of column 17-18). Godfrey et al. teach that there are many suitable toxin components (column 18 at lines 6-11), including the bacterial toxin ricin (column 18 at lines 6-11 in view of column 10 at lines 47-49).

Godfrey et al. teach that immunotoxins comprising anti-ACT-4 antibodies, including humanized anti-Act-4 antibodies, can be used as therapeutic reagents to suppress undesired immune responses by selectively eliminating activated CD4 T cells (see entire document, but especially column 22 at lines 11-36). Godfrey et al. teach that therapeutic agents which selectively eliminate activated cells are particularly advantageous because such reagents eliminate the cells involved in the undesired immune response while sparing non-activated T cells and preserving a residual immune capacity (see comments at column 22 lines 27-36).

Godfrey et al. review in column 2 the art-recognized motivation for developing multiple reagents which targeted different cell-surface receptors for use in methods of suppressing undesired immune responses. In particular, Godfrey et al. note that when using a single therapeutic agent to suppress an undesired immune response in a patient the patient may develop an immune response to the agent which prevents its effect and that cells expressing the target antigen may adapt to the therapy by ceasing to express the target antigen.

Finally, Godfrey et al. also note that the art recognized that while it was desirable to develop multiple reagents, the ideal reagents block only undesired immune responses while leaving a residual capacity to effect desirable immune responses (see especially comments at column 2, lines 7-40).

Kuchroo et al. teach monoclonal antibodies to human CTLA4 which bind to CTLA4 and prevent the interaction of B7 with human CTLA4 (see entire document, e.g., "Summary of the Invention" at columns 2-4). Kuchroo et al. teach that the anti-human CTLA4 monoclonal antibodies may be humanized (e.g., column 2 at lines 48-60 and columns 7-9). Kuchroo et al. review that CTLA4 is a molecule expressed only on activated T cells (see comment at column 1, lines 60-67). Kuchroo et al. further review that "B7" includes B7-1 and B7-2 (e.g., column 1 at lines 27-50). B7-1 is an alternate name for CD80 and B7-2 is an alternate name for CD86.

Kuchroo et al. do not teach an antibody-toxic moiety conjugate comprising a humanized monoclonal antibody that specifically recognizes human CTLA4, including wherein the antibody blocks binding of CTLA4 to CD80 or CD86.

The Examiner has previously argued that given the teachings of Godfrey et al. that it was desirable to produce toxins conjugated to different antibodies which each targeted different cell surface molecules expressed selectively on cells involved in undesired immune responses in order to eliminate the cells in vivo and the teachings of Kuchroo et al. of antibodies to the CTLA4 antigen expressed on activated T cells; it would have been obvious to the ordinary artisan at the time the invention was made to produce antibody-toxin moiety conjugates comprising the anti-CTLA4 antibodies of Kuchroo et al.

Specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Corp. v. Electro Materials Corp. of America 202 USPQ 22 (S.D. N.Y. 1979); and In re Burckel 201 USPQ 67 (CCPA 1979).

That Kuchroo et al. teach the enhancement of an immune response using anti-CTLA4 antibodies not conjugated to a toxic moiety does not alter the fact that Kuchroo et al. also teach that CTLA4 is molecule expressed only on activated T cells. Viewed in the context of the teachings of Godfrey et al., the ordinary artisan would have appreciated that even though in certain instances antibodies to CTLA4 may be used to enhance an immune response, CTLA4 could also serve as a target for the elimination of T cells when the T cells were participating in an undesired immune response.

As noted supra, Godfrey et al. teach that many different toxins are suitable for conjugating to antibodies, and points in particular to the bacterial product ricin (column 18 at lines 6-11). As also noted supra, the antibodies of Kuchroo et al. prevent the interaction of B7 with human CTLA4 (see entire document, e.g., "Summary of the Invention" at columns 2-4). In addition, the antibodies of Kuchroo, because they do prevent the interaction of B7 with human CTLA4 would also necessarily bind to a region of the CTLA4 molecule in spatial proximity to the site of CTLA4 binding to a costimulatory molecule. Similarly, binding of the antibodies of Kuchroo et al. would necessarily be modulated by a substitution in CTLA4 at position 83 of SEQ ID NO:2.

Applicant has argued that there was no reasonable expectation of success in combining the teachings of Godfrey et al. and Kuchroo et al. because ACT4 is a member of a different family of molecules than CTLA4 and ACT4 is "unique" among activation antigens.

The Examiner has previously noted that the ordinary artisan would have had a reasonable expectation of producing the instant antibody-toxic moiety conjugate given the availability of the anti-CTLA4 antibodies of Kuchroo et al. and the standardized techniques for conjugating any of a variety of toxic moieties to an antibody.

It is further noted that the instant claims are drawn to a product. The motivation of the ordinary artisan to produce the instantly claimed product would also not have been inhibited by the fact that CTLA4 and ACT4 belong to different receptor families or the "uniqueness" of ACT4. Antibody linked toxins to a variety of receptor families were well known in the art at the time the invention was made for depletion of various cell types. The identification of cell surface molecules expressed predominantly on activated T cells provided the ordinary artisan with an opportunity to selectively eliminate activated T cells, but spare T cells not involved in the undesired immune response. As noted supra, Godfrey et al. clearly teach the desirability of selective targeting, and the desirability of targeting more than one receptor.

As previously noted, Godfrey et al. teach that any of a number of toxins are suitable components of an antibody-toxic moiety conjugate (column 18 at lines 6-11).

Hamann et al. teach that calicheamicin is a potent toxin that can be conjugated to antibodies, including humanized antibodies, and used to eliminate cells expressing the antigen recognized by the antibody of the conjugate (see entire document, especially "Background of the Invention" at columns 6-20).

The Examiner maintains that it would therefore have been obvious to the ordinary artisan at the time the invention was made to substitute the carbohydrate calicheamicin for the toxin moiety of the antibody-toxin immunoconjugate taught by Godfrey et al. and Kuchroo et al. The ordinary artisan would have been motivated to make such a substitution in view of the recognized suitability of calicheamicin in antibody-toxin conjugates, and because Hamann et al. teach that calicheamicin is a potent toxin. Given the teaching of antibody- calicheamicin conjugates by Hamann et al., the ordinary artisan would have had a reasonable expectation that the antibodies of Kuchroo et al. could also be conjugated to calicheamicin to produce antibody-toxic moiety conjugate comprising an antibody that specifically recognizes CTLA4 and a toxic moiety that is the carbohydrate calicheamicin. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The amendments to the instant claims do not appear to alter the rejection of record. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments have not been fully persuasive.

16. Claims 14 and 15 appear to be allowable.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday to Thursday from 7:30 to 5:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (571) 272-0841 . Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9306.

PHILLIP GAMBEL

Phillip Gambel, Ph.D.
Primary Examiner
Technology Center 1600
January 26, 2004